PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/195 — **A1**

(11) International Publication Number: WO 91/11181

(43) International Publication Date: 8 August 1991 (08.08.91)

(21) International Application Number: PCT/US91/00750

(22) International Filing Date: 5 February 1991 (05.02.91)

(30) Priority data:

475,360	5 February 1990 (05.02.90)	US
495,354	19 March 1990 (19.03.90)	US

(71) Applicant: BRITISH TECHNOLOGY GROUP (USA) INCORPORATED [US/US]; 2200 Renaissance Boulevard, Renaissance Business Park, Gulph Mills, PA 19406 (US).

(72) Inventor: RUBIN, Leo ; 3 Lynne Court, Suffern, NY 10901 (US).

(74) Agent: MITCHARD, Leonard, C.; Nixon & Vanderhye, 2200 Clarendon Boulevard, 14th Floor, Arlington, VA 22201 (US).

(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: THYROID HORMONE CARDIAC TREATMENT

(57) Abstract

Thyroid hormones are of value for the manufacture of medicaments for treating patients undergoing a cardiovascular compromise such as cardiac arrest.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**ES**	Spain	**MG**	Madagascar
AU	Australia	**FI**	Finland	**ML**	Mali
BB	Barbados	**FR**	France	**MN**	Mongolia
BE	Belgium	**GA**	Gabon	**MR**	Mauritania
BF	Burkina Faso	**GB**	United Kingdom	**MW**	Malawi
BG	Bulgaria	**GN**	Guinea	**NL**	Netherlands
BJ	Benin	**GR**	Greece	**NO**	Norway
BR	Brazil	**HU**	Hungary	**PL**	Poland
CA	Canada	**IT**	Italy	**RO**	Romania
CF	Central African Republic	**JP**	Japan	**SD**	Sudan
CG	Congo	**KP**	Democratic People's Republic of Korea	**SE**	Sweden
CH	Switzerland			**SN**	Senegal
CI	Côte d'Ivoire	**KR**	Republic of Korea	**SU**	Soviet Union
CM	Cameroon	**LI**	Liechtenstein	**TD**	Chad
CS	Czechoslovakia	**LK**	Sri Lanka	**TG**	Togo
DE	Germany	**LU**	Luxembourg	**US**	United States of America
DK	Denmark	**MC**	Monaco		

THYROID HORMONE CARDIAC TREATMENT

This invention relates to the use of thyroid hormones and related compounds to facilitate cardiac resuscitation and enhance cardiac function.

Cardiac arrest occurs when there is electrical and mechanical dysfunction in the heart. The survival of cardiac arrest depends on timely defibrillation and the administration of proper medications. Standard treatments for cardiac arrest include the administration of various drugs appropriate to the variety of situations in which cardiac arrest occurs. However, a more effective treatment is clearly required in view of the current low survival rate and high annual morbidity from cardiac arrest.

Thyroid hormones include thyroxine [O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodotyrosine, T4], which is hereinafter referred to as thyroxine, and 3,5,3' triiodothyronine [O-(4-hydroxy-3-iodophenyl)-3,5-diiodotyrosine, T3], which is hereinafter referred to as triiodothyronine. Triiodothyronine is qualitatively similar to thyroxine in its biological effect but is more potent on a molar basis. Although some triiodothyronine is synthesized in the thyroid gland, the majority of the naturally occurring compound is synthesized through the metabolic conversion of thyroxine in peripheral tissues by the enzyme 5'-deiodinase.

Thyroxine is the sole thyroid hormone in clinical use today. This is largely due to its availability and relatively long half-life of 6 to 7 days which results from its avid binding to thyroxine-binding globulin in human serum and its consequent protection from metabolic breakdown and excretion. Pure triiodothyronine is not in clinical use due to its relative unavailability and less than avid binding to thyroxine-binding globulin which results in a half-life of two days or less.

Thyroxine has until now been shown to play a negative role in heart function.

It is possible for patients to suffer either from an excess or a deficit of thyroxine. Thyroxine increases the heart rate and the force of the beats, thus increasing cardiac output, and patients suffering from hyperthyroidism, caused by an excess of thyroxine, exhibit a number of cardiac dysfunctions such as heart palpitations, dyspnea, tachycardia, systolic hypertension and a variety of heart murmurs. The effects of hyperthyroidism on the heart may also include premature beats, auricular fibrillation, increased stroke volume and increased cardiac output, and although the peripheral vascular resistance decreases, the myocardial workload becomes greater. Hyperthyroidism may ultimately lead to angina, arrhythmias and heart failure.

Thyroxine is routinely used in treatment of patients lacking adequate thyroid function. Such patients are those with hypothyroidism (myxedema), goitre or cretinism.

Due to its effect on the heart, in current practice administration of thyroxine is contraindicated for patients with heart conditions such as tachyarrhythmias, acute myocardial infarction, cardiac instability and severe heart disease. Thyroxine can have serious cardiac effects even when given to patients without an underlying heart condition. Thus, Bacci et al, JAMA, 1981, 245, 920 report that a sudden, large load of thyroxine given to a hypothyroid patient with severe myxedema had a direct and rapid undesirable effect on the myocardium, causing cardiac arrest. Furthermore, thyroxine therapy for hypothyroidism has been reported by Bergeron et al, Arch. Intern. Med., 1988, 148, 1450, to have caused severe segmental left ventricular ischemic changes, subendocardial infarction and cardiogenic shock in a patient with a normal coronary anatomy.

Accordingly both in hyperthyroid patients who exhibit an excess of thyroid hormone in the body and in hypothyroid patients treated with thyroxine to correct a thyroid hormone deficiency in the body, thyroxine has been found to play a negative role in heart function. Despite this, it has now surprisingly been found that the administration of a thyroid hormone can effect cardiac

resuscitation in patients undergoing cardiac arrest. The effect of the thyroid hormone is rapid and can occur even where standard treatments have failed. Thyroid hormones have been found to effect both the chronotropic and ionotropic heart functions. This valuable function of thyroid hormones also extends into other areas of cardiovascular compromise than cardiac arrest.

Accordingly the present invention comprises the use of a thyroid hormone for the manufacture of a medicament for use in the treatment of a patient undergoing a cardiovascular compromise.

The various investigations reported in the literature concerning hyperthyroidism, hypothyroidism and the effects of the use of thyroxine do include papers by Kranz et al, Exp. Path. Bd., 1976, 12, 129, and by Gay et al, Am. J. Physiol., 1987, 253, H341, both of which describe a beneficial effect of thyroxine on the heart. Thus, Kranz et al report experiments with hyperthyroid and hypothyroid rats in which a myocardial infarction is artificially induced. It was found that wound healing in the heart for those rats which survived the myocardial infarction was better in the hyperthyroid rats than in the hypothyroid rats. Gay et al again artificially induced a myocardial infarction in rats, but in this case normal rats were used and those rats which survived the myocardial infarction were treated with thyroxine. Studies carried out 3 weeks after the infarction showed that rats treated with low doses of thyroxine, but not with higher doses thereof, showed an improvement in LV dysfunction as compared with control rats. However, neither of these papers contains any indication that thyroxine could be of value in treating a patient undergoing a cardiac compromise and in particular a patient undergoing cardiac arrest or otherwise requiring cardiac resuscitation, whereas it and other thyroid hormones have now been found to be effective in restoring or improving cardiac rhythm and function even in situations where standard treatments fail.

The term thyroid hormone used herein includes particularly compounds suitable for use in treating thyroid hormone deficiency in the body, i.e. any thyroid agonist. In general, the thyroid

hormones of use in the present invention are thyroxine and triiodothyronine and derivatives and analogues thereof, either singly or in combinations of two or more thereof. Thyroxine and triiodothyronine, and their derivatives and analogues will generally be used in the L-form, which is that exhibiting a greater level of thyroid hormone activity, although, less preferably, the L-form may be used together with the D-form, for example as the DL-racemate. Typically, preferred thyroid hormones of use in the invention will have an activity which is equal to or greater than that of DL-thyroxine, particularly of L-thyroxine. Triiodothyronine and its derivatives and analogues have the advantage, among others, of a higher level of activity as compared with thyroxine and its derivatives and analogues. L-Triiodothyronine is thus the preferred thyroid hormone for use in the present invention.

The thyroid hormones thyroxine and triiodothyronine are obtainable from natural sources such as bovine thyroid glands or may be synthesized in vitro, for example using chemical methods such as those described by Anthony et al in U.S. Patent 2,803,654. Various derivatives and analogues of these compounds also exert thyroid hormone activity as defined hereinbefore and may be used in the present invention. A group of such compounds and their methods of synthesis is described by Meltzer et al in U.S. Patent 3,109,024.

If desired, the thyroxine hormone may take the form of a physiologically acceptable salt. Thyroxine and triiodothyronine contain both an amino group and a carboxy group. It is, therefore, possible to form salts with both physiologically acceptable bases and acids. Examples of suitable bases are the alkali metal hydroxides, for example sodium hydroxide, quaternary ammonium hydroxides and amines such as tris (tris representing 2-amino-2-hydroxymethyl propane 1,3-diol). Suitable acids may be inorganic or organic. Examples of such inorganic acids are phosphoric acid, nitric acid, sulphuric acid and particularly the hydrohalic acids hydrochloric acid, hydrobromic acid and hydroiodic acid. Examples

of such organic acids are citric acid, oxalic acid, fumaric acid, maleic acid, lactic acid, succinic acid, malic acid, tartaric acid and methane sulphonic acid. Salts with bases are of particular interest and L-thyroxine is commonly marketed in the form of its sodium salt.

The present invention is of particular application in conditions of cardiovascular compromise which involve some degree of electrical and/or mechanical dysfunction. Moreover, its especial value is in the treatment of acute conditions of cardiovascular compromise. Nevertheless, the overall range of use is a wide one and specific examples of areas of use of the invention are when the patient undergoing the compromise is suffering from cardiac arrest, a bradyarrhythmia or electromechanical dissociation (EMD), has had a cardiopulmonary bypass or is in a mechanical cardiac support system with the thyroid hormone being used as adjunct therapy. Other specific examples of conditions of cardiovascular compromise in which the present invention may be applied occur when the patient undergoing the compromise is suffering from a cardiomyopathy, or an acute condition induced thereby, as well as when the patient is suffering from cardiac failure.

The present invention is perhaps of most value when the patient is undergoing cardiac arrest although it is also of value when the patient is suffering from a condition or undergoing a treatment such as those just described, especially if cardiac resuscitation is required. As regards these other areas of use, cardiomyopathies are the result of ischemic, metabolic or idiopathic disorders or are the result of microbial infections, such as those caused by viral, bacterial, fungal or parasitic infection, whilst bradyarrhythmias are caused by cardiovascular disease or arise post cardiac arrest. The use of the invention is also indicated in EMD which results post defibrillation or on myocardial infarction and occurs when the electrical and physical actions of the heart become dissociated so that the electrical stimulation no longer produces a concomitant physical movement.

The invention is of use in post-cardiopulmonary bypass, particularly when an attempt is made to restart the heart with epicardial defibrillation or when initial attempts are unsuccessful at restoring effective heart contraction. The medicament of the invention also finds use as adjunct therapy in a mechanical support system to enhance function of the heart and to offer support in situations including cardiopulmonary bypass and the use of a ventricular assist device or intraaortic balloon.

For cardiac resuscitation the thyroid hormone is administered directly into the heart cavity, parenterally or directly into the pulmonary system. In general, as an indication for injection, it may be stated that wherever epinephrine was previously utilized, thyroid hormones may now be used with advantage either to replace the epinephrine or in conjunction with it. Such cardiac resuscitation treatment is usually employed in the treatment of cardiac arrest, of electromechanical dissociation and in patients who have undergone a post cardiopulmonary bypass or who are on a mechanical cardiac support system.

Examples of these modes of administration are as follows. Direct administration into the heart may particularly involve direct intracardiac injection. Parenteral administration may involve a central venous line infusion via a pump or direct intravenous injection. Pulmonary administration may involve direct endotracheal injection (or infusion), such as through an endotracheal tube, or through an airway system, such as through a vaporizer, atomizer or an endotracheal tube.

For the treatment of patients with cardiomyopathies or bradyarrhythmias, the mode of administration may again be parenteral, by direct pulmonary infusion or even by intracardiac injection, but in these cases also extends to topical and gastrointestinal treatment. Parenteral and pulmonary administration may conveniently be as described hereinbefore whilst modes of topical application include the use of creams, ointments, gels, rinses and transdermal patches. Such applications are known in the art in other contexts, any physiologically acceptable base

in which thyroid hormones are at least partially soluble being suitable for topical use in the present invention. Transdermal patches are, for example, described by Chien et al in U.S. Patent 4,818,540.

The preferred dosage of thyroid hormone depends particularly on the specific activity of the thyroid hormone used. The dosage ranges may, however, generally be at a somewhat higher level than those usually employed when the hormones are used in other contexts such as the treatment of hypothyroidism, particularly when the medicament of the invention is used in cardiac resuscitation. Thus, for example, when used in treating hypothyroid patients L-thyroxine is usually given orally in pill form at a unit dosage level of 25 to 200 μg. However, in cases where oral administration of thyroxine is not possible or in an emergency such as where hypothyroidism has led to coma, L-thyroxine is administered parenterally, either intravenously or by intramuscular injection. Parenteral administration is usually at a similar dosage to that taken orally except in the case of emergency where up to 200 to 500 μg may be administered intravenously.

Although the dosages preferred for the medicament of the invention will vary even in the case of a particular thyroid hormone, depending on the condition being treated, it may be stated by way of guidance that in the case of L-thyroxine the dose for a human patient will often be in a range of 100 μg to 10 g when given parenterally in at least one rapid bolus injection with repeated injections of comparable amounts as necessary to attain and sustain hemodynamic stability. In the case of L-triiodothyronine the range for similar usage will usually be 1 μg to 1 mg. Veterinary usage, for example in mammals, will be on a similar ratio of thyroid hormone/body weight. Appropriate doses of other compounds may be calculated according to their relative activity to L-thyroxine and L-triiodothyronine in standard uses of these compounds. Variations within these ranges of dosages for the thyroid hormones will depend on the weight of the patient, the severity of the situation, the underlying pathology and, when cardiac arrest is involved, the time

from onset of the arrest with greater amounts being given as the time which has elapsed from cardiac arrest increases. When cardiac resuscitation is involved, as in the treatment of cardiac arrest, the more commonly used minimum dosage is 500 µg or 1 mg for L-tyroxine and 50 µg or 100 µg for L-triiodothyronine. Even in this case, a more common maximum for L-tyroxine will be somewhat less than 10 g, for example 1 g or 100 mg. It is preferred that patients undergoing cardiac resuscitation receive the thyroid hormone in conjunction with defibrillation although thyroid hormones may be administered in the absence of other therapy.

Patients who do not require cardiac resuscitation, such as those with cardiomyopathies and bradyarrhythmias, may often be treated with smaller doses, for example in the range of 100 µg to 500 µg daily of L-thyroxine or of 1 µg to 50 µg daily of L-triiodothyronine, the thyroid hormone preferably being administered gastrointestinally or topically.

Overdoses of thyroid hormones can if necessary be immediately aborted with intravenous doses of β-blockers, for example propanolol and metoprolol. Furthermore, when L-thyroxine is used in large doses subsequent treatment with β-blockers may be appropriate to prevent the effects of the induced hyperthyroid condition on the heart. On the other hand, if L-triiodothyronine is used, β-blockers may not be necessary or may be required only at lower levels as it is rapidly metabolized and/or excreted from the body. Thus, even though it has not heretofore been used clinically, L-triiodothyronine and its derivatives and analogues are preferred over L-thyroxine and its derivatives and analogues as the former are more active on a molar basis and give rise to fewer hyperthyroid symptoms. Thus L-triiodothyronine is approximately four times as potent as L-thyroxine whilst the 3'-isopropyl,-3,5-diiodo-thyronine analogue is approximately seven times as potent.

For the most part, the medicaments prepared according to the present invention may take conventional forms, and may be formulated in unit dosage form where desired, i.e. in the form of discrete portions each comprising a unit dose, or a multiple or

sub-multiple of a unit dose, for example 100 µg, 500 µg, 1 mg, 10 mg, 100 mg, 1 g or more for L-thyroxine and 50 µg, 100 µg, 250 µg, 500 µg or more for triiodothyronine. It will be appreciated from the foregoing discussion that certain of the unit dosage formulations will be novel per se.

In general, the medicament may incorporate a liquid diluent or carrier, for example an aqueous or oily suspension, emulsion or particularly solution, which may often be employed in injectable or infusable form for parenteral administration or pulmonary administration and therefore may conveniently be sterile and pyrogen free. For parenteral use thyroxine is preferably supplied in lyophilized form and is reconstituted, for example with saline, immediately prior to use.

Where oral administration is used the medicament may incorporate a liquid diluent or carrier, although it is more usual to use a solid, for example a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate. Such solid compositions may conveniently be of a formed type, for example as tablets, capsules (including spansules), etc.

Moreover, as indicated hereinbefore, topical formulations may be used including creams, rinses, gels and transdermal patches.

However, apart from certain unit dosage formulations, there are other modes of presentation of the medicaments of this invention which are novel per se.

The present invention thus includes a kit suitable for administration of a thyroid hormone to a patient undergoing a cardiovascular compromise, particularly a patient undergoing cardiac arrest. Such a kit comprises a thyroid hormone in a physiologically acceptable liquid diluent or carrier or in a solid form suitable for formulation in such a liquid diluent or carrier prior to use (which liquid diluent or carrier may then optionally form a separate part of the kit) together with a device for the injection of the thyroid hormone. The solid form may conveniently consist of powdered or lyophilized material. The liquid diluent or carrier may, for example, be saline or another liquid which

provides a solution of the hormone and is physiologically acceptable. An example of a suitable injection device is one based on the Abboject "Unit of Use Syringe" supplied by Abbott Laboratory which delivers a single dose of adrenalin to the heart via an intracardiac needle.

The present invention further includes a device suitable for pulmonary infusion of a thyroid hormone to a patient undergoing a cardiovascular compromise, particularly a patient undergoing cardiac arrest. Such a kit comprises atomizer or vaporizer means containing a thyroid hormone in a physiologically acceptable liquid diluent or carrier.

As indicated previously, the medicament can contain more than one thyroid hormone and, in addition, may optionally contain other substances which are therapeutically effective in enhancing the function of the heart, for example a suitable formulation of one or both of magnesium and calcium. It is also possible for the thyroid hormone to be used in conjunction with epinephrine and if desired the two compounds may be formulated together.

The invention is illustrated by the following Examples which describe the use of L-thyroxine to treat dogs in which cardiac arrest has been artifically induced. It will be seen from the examples that L-thyroxine restored normal cardiac function even where standard methods had failed and did not cause any symptoms of hyperthyroidism in the treated dogs. However, since dogs lack thyroxine-binding globulin, L-thyroxine is rapidly metabolized or excreted after administration. In humans, L-thyroxine persists up to a week after treatment and for this reason its effects are often counteracted by β-blockers administered subsequently to the thyroxine treatment. On the other hand, L-triiodothyronine does not bind avidly to thyroxine-binding globulin and the effect in humans of this preferred thyroid hormone thus directly correlates with the observed effect of L-thyroxine in dogs.

Example 1

Using a Ventritex bedside, external pulse generator and defibrillator, rapid pacing at a rate of 30-50 milliseconds for approximately 4-6 seconds was used to induce ventricular fibrillation in a mongrel dog weighing 30-50 pounds.

Defibrillation threshold in the dog was established by repeated attempts at fibrillation and defibrillation via the Ventritex pulse generator according to the manufacturer's instructions. During one episode while attempting to determine threshold defibrillation, standard shock (250 volts (V)) and "rescue shock" (950 V) were ineffective. Large energy pulses were then applied via an external defibrillator (Hewlett Packard), resulting in cardiac standstill as determined by electrocardiographic monitoring. The dog was then paced with 10 V of 1 millisecond duration at a rate of 100 beats per minute (bpm).

Every attempt at turning off the pacing unit resulted in returning the rhythm to standstill as evidenced by ECG and lack of palpable pulse. After approximately three minutes of cardiac standstill without any effective rhythm, the dog was given an intravenous bolus of 250 µg of L-thyroxine (obtained from Stris Laboratories Inc., Arizona, and prepared according to the manufacturer's instructions). Approximately 1-1.5 minutes after receiving the L-thyroxine the dog reverted to normal cardiac rhythm with a good palpable pulse.

Example 2

After establishing defibrillation threshold as described in Example 1, external defibrillation was administered eight times as in Example 1, without establishing normal cardiac rhythm. The dog was then given an intravenous bolus injection of 250 µg of L-thyroxine. Approximately 1 minute after receiving the L-thyroxine the dog developed a spontaneous rhythm alternating between sinus and supraventricular. The dog subsequently developed A-V dissociation, and was given a second intravenous bolus injection of 250 µg of L-thyroxine upon which the dog reverted to normal cardiac rhythm with an effective pulse. The dog maintained a sinus rhythm and good pulse until it was sacrificed.

Example 3

A dog was put into fibrillation and the defibrillation threshold was obtained as described in Example 1. Throughout the experiment the dog was on a ventilator to maintain oxygenation. Defibrillation was attempted at 250 V without effect. A rescue shock of 950 V was then applied as in Example 1 without effect. The 950 V shock was repeated 23 times without effect. At this point the dog's chest was opened and a shock was applied directly to the heart with internal epicardial paddles at 400 joules using a Hewlett Packard defibrillator as per the manufacturer's instructions.

After the direct cardiac stimulation the dog briefly came out of fibrillation but immediately returned to ventricular fibrillation with no apparent mechanical activity. The heart was again stimulated with internal epicardial paddles at 400 joules and the dog reverted to a tachyarrhythmia with electromechanical dissociation which then degenerated to ventricular fibrillation. The dog was then shocked with 950 V externally and defibrillation persisted. At this point, about 8.5 minutes after initial onset of fibrillation, L-thyroxine was administered in a bolus of 250 µg given by intracardiac injection. After approximately 100 seconds and four defibrillation attempts the dog developed atrioventricular dissociation and subsequently reverted to a super ventricular tachyardia with electromechanical dissociation. A second intravenous bolus of 250 µg of L-thyroxine was then administered and in less than 20 seconds the dog developed an effective pulse and rapidly reverted back to a sinus rhythm. The following morning the dog was alert and ate well.

CLAIMS

1. The use of a thyroid hormone for the manufacture of a medicament for use in the treatment of a patient undergoing a cardiovascular compromise.

2. The use according to Claim 1, in which the thyroid hormone is thyroxine or triiodothyronine or an analogue or derivative thereof.

3. The use according to Claim 1, in which the thyroid hormone is thyroxine.

4. The use according to Claim 1, in which the thyroid hormone is triiodothyronine.

5. The use according to any of Claims 1 to 4, in which the patient undergoing cardiovascular compromise is suffering from cardiac arrest, a cardiomyopathy, a bradyarrhythmia or electromechanical dissociation, has had a cardio-pulmonary bypass, or is in a mechanical cardiac support system.

6. The use according to Claim 5, in which the patient is undergoing cardiac arrest.

7. The use according to any of Claims 1 to 6, in which the patient is treated with the medicament by direct injection into a heart cavity, by direct pulmonary administration, parenterally, gastrointestinally or topically.

8. The use according to Claim 7, in which the medicament is used to effect cardiac resuscitation, being administered by direct injection into a heart cavity, by direct pulmonary administration or by parenteral administration.

9. The use according to Claim 7 or 8, in which the direct pulmonary administration is by direct endotracheal injection or infusion through an airway system and the parenteral administration is by central venous line infusion or by direct intravenous injection.

10. The use according to Claim 3 or any of Claims 5 to 9 as dependent on Claim 3, in which the patient is treated with a dose of the medicament which is in the range of 100 μg to 10 g.

11. The use according to Claim 4 or any of Claims 5 to 9 as dependent on Claim 4, in which the patient is treated with a dose of the medicament which is in the range of 1 µg to 1 mg.

12. The use according to any of the preceding claims, in which the medicament contains, as a further active component thereof, one or both of magnesium and calcium.

13. A kit comprising a thyroid hormone in a physiologically acceptable liquid diluent or carrier or in solid form and a device for the injection thereof.

14. Atomizer or vaporizer means containing a thyroid hormone in a physiologically acceptable diluent or carrier.

15. A kit according to Claim 13 or atomizer means according to Claim 14, in which the thyroid hormone is as defined in any of Claims 2, 3 and 4.

16. A kit according to Claim 13 or 15 or atomizer means according to Claim 14 or 15 which additionally contains one or both of magnesium and calcium.

17. A pharmaceutical composition in unit dosage form which comprises thyroxine in a dosage of greater than 500 µg.

18. A pharmaceutical composition in unit dosage form which comprises triiodothyronine in a dosage of greater than 50 µg.

19. A pharmaceutical composition for treating a patient undergoing a cardiovascular compromise which comprises a thyroid hormone.

20. A process for preparing a medicament for treating a patient undergoing a cardiovascular compromise which comprises incorporating therein as an active ingredient a thyroid hormone.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/00750

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 31/195

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	FR, A, 2354101 (BEREMA S.A.) 6 January 1978 see claims	17-20
X	WO, A, 8907454 (SMITH and WESSLAU) 24 August 1989 see page 2, lines 29-34,7,8; page 3, lines 17-21; examples 1,2; page 4, lines 34-37; claims	13-15,17-20
X	Patent Abstracts of Japan, vol. 12, no. 306 (C-522)(3153), 19 August 1988, & JP, A, 6379824 (ADVANCE CO. LTD) 9 April 1988 see the abstract	13,17,18
X	Rote Liste, 1989, Editio Cantor, (Aulendorf/Württ., DE), no. 73001-73013 see no. 73008	13,18

./.

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report:
20th May 1991	26. 07. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme. M. van der Drift

Form PCT/ISA/210 (second sheet) (January 1985)

International Application No PCT/US 91/00750

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Acta Med. Scand., vol. 222, 1987, B. Hylander et al.: "Long-term ECG recordings in thyroxine-substituted hypothyroid subjects", pages 429-432 see the whole article --	1-20
A	Annales & Endocrinologie, vol. 44, no. 4, 1983, Masson, (Paris, FR); U. Paschen et al.: "Alteration in thyroid hormone concentration during and after coronary bypass operation", pages 239-242 see the whole article --	1-20
A	Diabetes, vol. 37, November 1988, H. Xiang et al.: "Effect of myo-inositol and T3 on myocardial lipids and cardiac function in streptozocin-induced diabetic rats", pages 1542-1548 see the whole article --	1-20
X	American Journal of Physiology, vol. 226, no. 1, January 1974, (US), M.J. Goodkind et al.: "Effect of thyroxine on ventricular myocardial contractility and ATPase activity in guinea pigs", pages 66-72 see the whole article	1-12
